Carbohydrate Research 344 (2009) 1282–1284

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis of 3-azido-3-deoxy-β-D-galactopyranosides

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ARTICLE INFO

Article history:
Received 30 March 2009
Accepted 7 May 2009
Available online 9 May 2009

Keywords:
Galactose
Gulose
Epimerization
Azide

ABSTRACT

Three efficient routes to 3-azido-3-deoxy-β-D-galactopyranosides were developed relying on a double inversion protocol at C3. Two of the routes were demonstrated to work with both O- and S-glycosides. In all three routes, the 2-*O*-acetyl-3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-galactopyranosides were obtained by an azide inversion of the key intermediates 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-trifluoromethanesulfonyl-β-D-gulopyranosides. The intermediate gulopyranosides were in turn obtained from 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-trifluoromethanesulfonyl-β-D-galactopyranosides, installed in one pot from the 4,6-*O*-benzylidene-β-D-galactopyranosides, by inversion with nitrite or acetate. For O-glycosides, the gulopyranoside configuration could alternatively be obtained from the 4,6-*O*-benzylidene-β-D-galactopyranoside by elimination to give the 2,3-dianhydro derivative followed by a highly stereoselective cis-dihydroxylation.

1. Introduction

D-Galactopyranose is ubiquitous to mammalian glycoconjugates, where it can be glycosidically linked via O1–O4 and O6 oxygen atoms. The HO2 is fucosylated in blood group determinants, the HO3 is glycosylated with various monosaccharides, including sialic acid, as well as sulfated, HO4 is glycosylated with β-D-GalNAc or α-D-Gal in the ganglio- and globo-series of glycolipids, HO6 is sialylated or sulfated in glycolipid or glycoprotein glycans. The diversity of galactose glycosylation and modification in mammalian glycoconjugates most often play critical roles in controlling the function of the glycoconjugate. The chemical properties of the glycosidic atom linked to galactopyranose can be expected to influence conformational preferences, as well as interactions with, for example, proteins, which in turn affects biological activities. Hence, replacement of oxygens of glycosidic bonds involving galactopyranose with other atoms is an important strategy for deciphering the biological importance of the glycosidic oxygens in galactose-containing glycans. Within this context, various oxygen replacements of HO3, HO4, and HO6 have been reported, while HO2 oxygen replacements are less frequent. Galactose HO4 have been readily prepared, for example, by substituting glucose 4-O-sulfonate leaving groups with nucleophiles.[1,2] Galactose HO6 is maybe even more readily accessible via substitutions of a, for example, galactose 6-O-sulfonate. In contrast, replacement of the galactose HO3 oxygen is more challenging. A reliable route for replacement of this oxygen starts from di-isopropylidene-D-glucofuranose in which C3 is doubly inverted together with a single inversion at C4. This route has been used, for example, in the synthesis of 3-amino-gal-UDP, which still is one of the most potent GalT inhibitors reported to date.[3] Synthesis strategies toward ganglioside GM_3 analogs incorporating a galactose 3-thio linkage were developed based on the discovery that 4,6-*O*-benzylidene-2-*O*-acyl-β-D-galactopyranoside derivatives readily undergo double inversions at C3 and thus, via the gulo-epimer, provide access to the galactose 3-thio analogs that either act as neuraminidase inhibitors[4,5] or can be used as vaccine constituents with improved hydrolytic stability.[6] More recently, the Ramström group has made substantial contributions to our general understanding of the influence of protecting group pattern, relative configuration, solvent, and nucleophile on carbohydrate hydroxyl inversion efficiency, which in turn has led to the development of highly efficient and practical protocols for carbohydrate epimerizations including C4.[7–9]

We have reported on efficient galectin inhibition with galactose 3C-amides or 3C-triazoles.[10–16] These inhibitors have all been derived from the 3-azido-3-deoxy-galactopyranose originally described by Lowary and Hindsgaul[3] and later developed into a thioglycoside donor by us.[10] However, the synthesis of 3-azido-3-deoxy galactosides from di-isopropylidene-D-glucofuranose involves several steps of which a majority requires column chromatography for purification of intermediates, PCC oxidations, and hydrogenations that are laborious on large scale. This prompted us to investigate the possibility to introduce the 3-azido-functionality by double inversions at C3 of 4,6-*O*-benzylidene-β-D-galactopyranosides. Apart from being potentially more efficient and easier to handle on large scale, this route would allow for installation of

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doi:10.1016/j.carres.2009.05.005

an O- or S-glycoside aglycon prior to 3-azido introduction. Herein, we report on the evaluation and optimization of two alternative double inversion protocols at C3 of 4,6-*O*-benzylidene-β-D-galactopyranosides that are efficient routes toward 3-azido-3-deoxy galactopyranosides.

2. Results and discussion

2.1. O-Glycosides

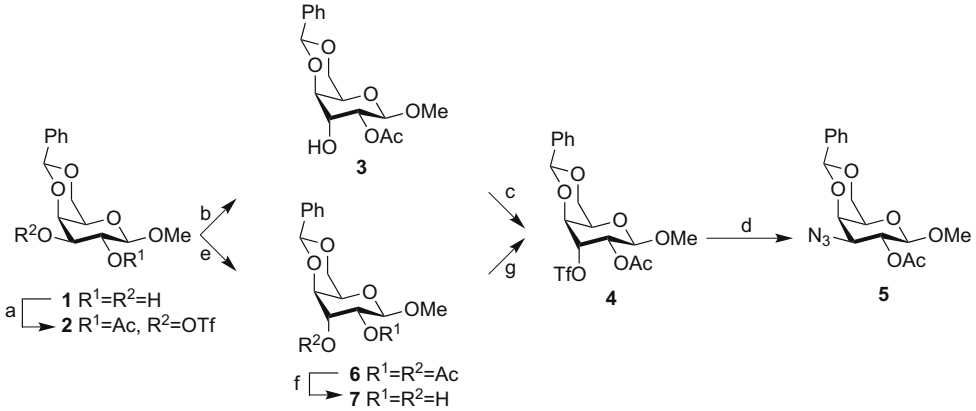
First, two closely related routes to methyl 2-acetyl-3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-galactopyranoside **5** were investigated. Both routes started with activation of HO3 of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside **1** by triflation, followed by acylation of HO2, in a high-yielding one-pot reaction: Treatment of **1** with triflic anhydride in dichloromethane/pyridine,[17] followed by addition of acetyl chloride provided the triflate **2** (Scheme 1). The crude triflate **2** was immediately treated with tetrabutylammonium nitrate to give the gulo-derivative **3** in 60% from **1**. Triflation of **3**, followed by immediate treatment of the crude gulo-triflate **4** with tetrabutylammonium azide gave the 3-azido-3-deoxy-galactoside **5** in 62% from **3**.

In the second alternative route, the first inversion with the galacto-triflate was done with cesium acetate to give the diacetate **6** (Scheme 1). The inversion with cesium acetate to give **6** was somewhat higher yielding than the corresponding inversion with sodium nitrite to give **3**. However, this advantage was to some extent counter-balanced by the need for two extra steps to reach the gulo-triflate **4** necessary for azide introduction. Nevertheless, these two extra steps, deacetylation to give the dihydroxy compound **7** and then selective HO2-acetylation and HO3-triflation toward **4**, were indeed uneventful and proceeded in high yields. Acetylation of **7** with one equivalent of acetyl chloride at ambient temperature proceeded with high selectivity for HO2 and addition of triflic anhydride at −10 °C provided the triflate **4**. The crude triflate **4** was immediately converted into the 3-azido-3-deoxy-galactoside **5** in a 72% yield from **7**. The higher yield in going from **7** to **5**, as compared to going from **3** to **5**, is unexpected, because the route **7** to **5** passes through **3** as an intermediate. We believe that the explanation is in the different scale the reactions were performed under. Route **3** to **5** was performed in 0.3 mmol scale and route **7** to **5** in 13.6 mmol scale. Typically, triflation yields increase with the scale of the reaction.

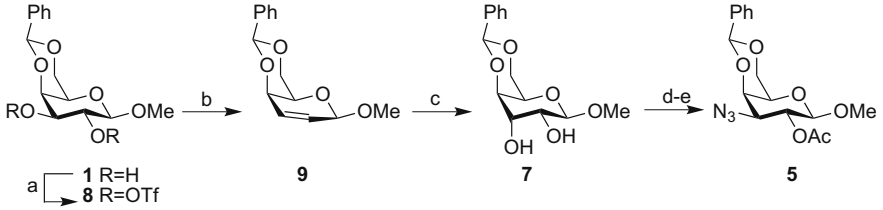
An alternative third double inversion route was envisioned possible via the readily accessible 2,3-dianhydro galactoside **9**, which should give gulopyranosides upon dihydroxylation. Hence, **1** was instead treated with excess triflic anhydride to give the 2,3-di-triflate **8**, which was immediately eliminated in a zinc-free Tipson–Cohen[18,19] reaction to give the 2,3-dianhydro galactoside **9** in high yield (Scheme 2). Cis-dihydroxylation under Upjohn conditions[20] of **9** afforded the expected C3-inverted gulo compound **7** (79 %), as the only observed diastereomer, together with unreacted **9** (21%). Compound **7** was converted into the target azide **5** as described above.

2.2. S-Glycosides

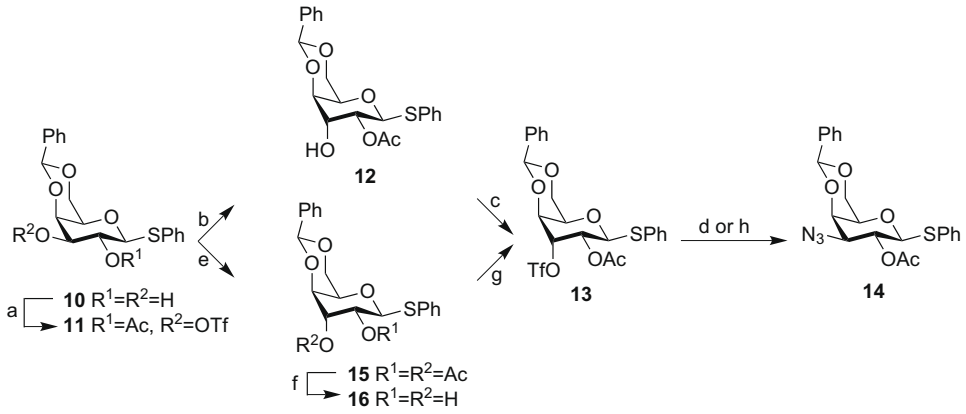
Although the double inversion route via the 2,3-dianhydro compound **9** (Scheme 2) was deemed more practical and more efficient than the double inversion via the two triflates **2** and **4** (Scheme 1), it was not applicable to thioglycosides, which was probably due to their sensitivity to the formation of thiophilic iodine during the sodium iodide-mediated elimination (as described for **8** to give **9**). Furthermore, the oxidative conditions required to generate the guloside **7** from **9** are generally not compatible with thio-glycosides. Hence, synthesis of 3-azido-3-deoxy-1-thio-β-D-galactopyranosides, for example, for use as galactosyl donors, was only possible via sequential inversion of O3 galacto and gulo triflates according to routes 1 and 2 described above for the corresponding methyl galactoside **5**. Applicability of routes 1 and 2 was demon-



Scheme 1. Reagents and conditions for routes 1 and 2: (a) i. Tf_2O, pyridine, CH_2Cl_2, −10 °C, ii. AcCl; (b) QNO_2, DMF, 50 °C (60% from **1**); (c) Tf_2O, pyridine, CH_2Cl_2, −10 °C; (d) QN_3, DMF, 50 °C (62% from **3**, 72% from **7**); (e) CsOAc, DMF (81% from **1**); (f) NaOMe, MeOH (92%); (g) [i]AcCl, pyridine, CH_2Cl_2, rt, [ii]Tf_2O, −10 °C.



Scheme 2. Reagents and conditions for route 3: (a) Tf_2O, pyridine, CH_2Cl_2, −10 °C (95%); (b) NaI, DMF, imidazole (95%); (c) OsO_4, NMO, DABCO, $MsNH_2$, CH_2Cl_2 (79%); (d) i. AcCl, pyridine, CH_2Cl_2, rt, ii. Tf_2O, −10 °C; (e) QN_3, DMF, 50 °C (72% from **7**).



Scheme 3. Reagents and conditions for routes 1 and 2 applied onto phenyl 1-thio-β-D-galactopyranoside: (a) i. Tf_2O, pyridine, CH_2Cl_2, −10 °C, ii. AcCl; (b) QNO_2, DMF, 50 °C (60% from **10**); (c) Tf_2O, pyridine, CH_2Cl_2, −20 °C; (d) QN_3, DMF, 50 °C (59% from **12**); (e) CsOAc, DMF (77% from **10**); (f) NaOMe, MeOH (98%); (g) i. AcCl, pyridine, CH_2Cl_2, rt, ii. Tf_2O, −10 °C; (h) NaN_3, DMF, 50 °C (42% from **16**).

Table 1
Summary of routes to 3-azido-galactose derivatives

Route	No of rxns	No of chrom.	Total yield (%)
Literature route[a]	11[21–23,3,10,15]	9	36[b]/19[c]
Route 1, Scheme 1	4	2	36
Route 2, Scheme 1	5	3	53
Route 3, Scheme 2	5	2	51
Route 1, Scheme 3	4	2	25[d]/35[e]
Route 2, Scheme 3	5	2	32

[a] From di-isopropylidene-D-glucofuranose to methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-1-thio-β-D-galactopyranoside.[21–23,3,10,15].
[b] The best overall yield possible by combining the literature reports and our own results.
[c] The best overall yield in our hands.
[d] NaN_3 was used in step h.
[e] QN_3 was used in step d.

strated by conversion of the phenyl 4,6-benzylidene-1-thio-β-D-galactopyranoside **10** into the phenyl 2-*O*-acetyl-3-azido-4,6-benzylidene-3-deoxy-1-thio-β-D-galactopyranoside **14** in good overall yields (Scheme 3). The yield of **14** could be improved by using tetrabutylammonium azide (compare Scheme 1), however for larger scale we prefer using sodium azide for safety and cost reasons despite the slightly lower yield.

3. Summary

A comparison of the original route from the commercial di-isopropylidene-glucofuranose with the herein presented routes from commercial methyl 4,6-benzylidene-β-D-galactopyranoside **1** and phenyl 4,6-benzylidene-1-thio-β-D-galactopyranoside **10** is presented in Table 1.

4. Concluding remarks

In conclusion, 3-azido-3-deoxy-β-D-galactopyranosides can be synthesized in few steps and in high yields via double inversion of 4,6-*O*-benzylidene-β-D-galactopyranosides. The route based on cis-hydroxylation of 2,3-dianhydro-β-D-galactopyranosides is faster, more practical, and preferable for the preparation of 3-azido-3-deoxy-β-D-galactopyranosides. However, another route based on sequential inversion of galacto and gulo 3-*O*-triflates is preferred if 1-thio-β-D-galactopyranosides are the desired product. Hence, the two routes complement each other and both serve as attractive alternatives to the more common literature procedure from di-isopropylidene-D-glucose. Although, the double inversion protocols herein are demonstrated with azide ion as the second nucleophile, we envision that reaction of **4** and **13** using other nucleophiles, such as halides, sulfur or carbon-based nucleophiles, will allow for efficient preparation of other 3-deoxy-galactoside derivatives.

Acknowledgments

We thank Lund University, the Swedish Research Council, the programs 'Glycoconjugates in Biological Systems' (GLIBS), and 'Chemistry for Life Sciences' sponsored by the Swedish Strategic Research Foundation for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.05.005.

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